

TITLE OF INVENTION

CHRONOTHERAPEUTIC FORMULATIONS OF DILTIAZEM AND THE
ADMINISTRATION THEREOF

JWAI 5 FIELD OF INVENTION

This invention relates to once daily preparations comprising Diltiazem and pharmaceutically acceptable salts thereof, such as the hydrochloride salt, suitable for evening administration to patients suffering hypertension and/or angina. This invention also relates to a method for evening administration of such once daily preparations to patients for the treatment of the patients' hypertension and/or angina.

BACKGROUND OF THE INVENTION

Diltiazem, a benzothiazepine, is an orally active calcium channel blocker (calcium-antagonist) with relatively high selectivity for vascular smooth muscle that is effective in the treatment of hypertension and angina pectoris. Today, persons having these conditions take prescribed once daily preparations of Diltiazem generally to maintain constant levels of the drug in the body over a 24-hour period. Until recently the timing of the taking of the medicine wasn't considered an important consideration by the medical community. Doctors generally did not take into account the natural circadian variation in the body's physiological functions. Researchers have now found that the timing of the taking of a medicine can affect the way the human body responds to the medicine. The science of treating the human body taking into account the natural circadian variation is Chronotherapeutics. Chronotherapeutics relies on the practice of delivering the correct amount of medication to the correct site of action at the most appropriate time period for the particular disease or condition.

In man, blood pressure does not remain constant during day and night. Early in the morning blood pressure begins to rise from the low levels reached during sleep. Increases in blood pressure are accompanied by increases in heart rate caused by the chemicals generated by the body and delivered into the blood stream. Epidemiological studies have indicated that the greatest incidence of heart problems such as stroke, heart attack, myocardial ischemia and sudden cardiac death occur during the early morning waking hours when the blood pressure is rising in response to the natural circadian rhythm. After normally rising in the morning, blood pressure remains elevated during the day until generally early evening when it starts to fall to its lowest level during sleep.

In one study, evening medication with Diltiazem for treatment of hypertension for effect the next morning has been stated to be more efficacious than other dosage schedules. *Administration Time - Dependent Effects of Diltiazem on The 24-Hour Blood Pressure Profile of Essential Hypertension Patients*, Isao Kohno et al. (Chronobiology International 14(1), 71-84, (1997.) In the report of the study, Herbesser R™ (200mg) was identified as the Diltiazem preparation. Herbesser R™ is a Diltiazem formulation comprising a mixture of immediate release diltiazem - containing microspheres and sustained release diltiazem - containing coated microspheres. According to the report, following a single dose (200 mg) administration, the time of peak plasma diltiazem concentration occurred at 12.5 hours after administration. The peak plasma diltiazem concentration Cmax in the persons studied was 107mg/ml. Following multiple dosages of 200 mg Diltiazem given over 7 days, the time of peak plasma diltiazem concentration (Cmax) was at 10 hours after administration. Cmax was 154 mg/ml.

However a careful review of the report shows inconsistencies which cannot support the authors' conclusions. Particularly at page 80, the best results shown in the graph are with respect to morning treatment with this formulation.

Moreover at page 82, the authors themselves acknowledge the study cannot lead

5 to reliable conclusions "because the number of patients was too small". Further, an immediate release portion of the dosage in the order of 15% is not desirable for evening administration. When the blood pressure is naturally at its lowest, not only is there no need for further reduction at that time, but such reduction can harm the patient. Particularly, if the blood pressure is reduced below a
10 minimum the patient is put at a greater risk for cardiovascular accidents including stroke. Further, the 15% immediate release diltiazem is no longer available when needed.

In *A comparative study of the steady-state pharmacokinetics of immediate-release and controlled-release diltiazem tablets*, O. R. Leeuwenkamp et al., Eur. J. Clin.

15 Pharmacol (1994) 46:243-247, controlled release properties and relative systemic availabilities of two dosages of the same controlled release diltiazem tablet formulation were studied by comparing them as steady state with those of an immediate release formulation. In the testing, the diltiazem plasma concentration increased slowly from about 6 hours after the evening dose of both
20 CR tablets (Diltiazem CR 90mg and Diltiazem CR 120 mg) resulting in relatively high plasma concentrations in the early morning hours. The clinicians concluded that twice-daily treatment with diltiazem CR tablets can replace thrice-daily treatment with a conventional diltiazem IR tablet. According to the clinicians "The early morning rise of the diltiazem plasma concentration, which might lead

to a lower incidence of ischemic events, may be an important clinical advantage of both CR tablets."

On April 22, 1998, Searle Canada announced that its Chronovera (R) (controlled onset extended-release verapamil) a high blood pressure medication was now

5 available in Canada. Chronovera (R) was, according to Searle Canada, specifically designed to work with the body's natural circadian variations and was designed to be taken once-a-day just before bedtime. Chronovera provided

24-hour blood pressure control but was designed to deliver peak concentrations of verapamil in the morning when the blood pressure, heart rate and incidence of

10 cardiovascular events were highest. According to Searle Canada, simply changing the time you take the drug your physician has prescribed will not provide the same safety and effectiveness that is designed specially for chronotherapy using verapamil. According to Searle Canada, its Chronovera (R)

is unlike traditional medications including extended-release (XL) and sustained-

15 release (SR) formulations which are usually prescribed in doses that maintain relatively constant levels of the drug in the body over a 24-hour period or attempt to maintain relatively constant levels of the drug in the body over a 24-

hour period. According to Searle Canada, the prior formulations do not take into account the natural circadian variations in the body's physiological functions.

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Sustained-release, once-daily diltiazem formulations have been taught which may be considered the traditional medication (according to Searle Canada). They appear not to give the benefits meant to be achieved by chronotherapy.

For example, in *Pharmacokinetic Properties and Antihypertensive Efficacy of Once-*

25 *Daily Diltiazem*, J. G. Kelly et al., Journal of Cardio-Vascular Pharmacology,

17:6:957-963, (1991), the controlled-release formulation of diltiazem released a proportion of the diltiazem relatively rapidly with the remainder released over a period extending to 24-hours. During *in vitro* dissolution testing 15% of the diltiazem in the dosage form was released in the first two hours, 54% was
5 released in the first six hours, 89% in the first 13 hours and all of the remainder was released between 13 and 24 hours after administration. The diltiazem capsules contained either 120 mg or 240 mg of diltiazem. It should be noted that no difference is shown between the placebo and dosages in the article at wake-up (between 5:00 a.m. and 8:00 a.m.).

10 U.S. Patent 4,960,596 discloses slow release 12 hour diltiazem formulations whose dissolution, when measured in accordance with United States Pharmacopoeia 21, purports to be within broad limits (between 5% and 35% after one hour, between 15% and 40% after two hours, between 20% and 50% after three hours, between 30% and 75% after four hours, between 40% and 80% after six hours and between
15 55% and 95% after eight hours). The examples in the patent, however, provide more specific range limitations specifying range limitations for the formulations exemplified such as at column 4, lines 8-10 and column 5, lines 60-62. In the first series of examples the release into aqueous medium was measured using the method of USP No. 21 of 10%-20% after one hour, 30%-35% after four hours and
20 60%-75% after eight hours. In the later examples, the release into aqueous medium was measured using the method of USP No. 21 at 15%-35% after one hour, 55%-75% after four hours, 75%-95% after eight hours. These formulations were, however, twice a day (b.i.d.) formulations.

A series of patents have issued to Elan Corporation p.l.c. involving controlled
25 absorption diltiazem pellet formulations for oral administration in which each

pellet has a core comprising diltiazem or a pharmaceutically acceptable salt thereof in association with a specified organic acid covered by an outer membrane which permits release of diltiazem from aqueous medium in accordance with U.S. Pharmacopoeia XX (Paddle Method) in buffered media at 5 pH 1.5, pH 4.0 and pH 7.0. These are U.S. Patent 4,721,619; 4,891,230; 4,894,240; 4,917,899; 5,002,776; 5,219,621; 5,336,504; 5,364,620 and 5,616,345.

In U.S. Patent 4,721,619, dissolution rates of the pellets of examples are found at column 4, lines 41-49 and column 5, lines 5-12. The formulations, however are for 12 hour. The formulations of U.S. Patents 4,891,230 are also for 10 administration every 12 hours.

U.S. Patent 4,894,240 purports to provide formulations for once-daily administration and specifies a general dissolution pattern at column 2, lines 43-52 and a more restricted dissolution pattern at column 3, lines 3-12. The dissolution rates are determined according to U.S. Pharmacopoeia XXI in 0.05M KCl at pH 15 7.0 and at 100 r.p.m. The examples of the patent, however, provide a more limited dissolution pattern under U.S. Pharmacopoeia XXI (Paddle Method) at column 7, lines 30-34 and 47-51, at column 8, lines 16-20, 32-36 and 49-53 and at column 8, line 66 - column 9, line 5. Similar examples are provided at columns 9, 10, 11 and 12. Nothing is taught with respect to formulations suitable as 20 chronotherapeutics.

U.S. Patents 4,917,899, 5,364,620 and 5,616,345 are to the same effect. So are the remaining Elan patents. Nothing in these patents teach formulations suitable as chronotherapeutics.

U.S. Patent 5,529,790 purports to teach a delayed sustained-release 25 pharmaceutical preparation in which a water-soluble drug core is surrounded by

a hydratable diffusion barrier which delays drug release for about two to ten hours. While diltiazem hydrochloride dissolution patterns were provided in accordance with the U.S.P. basket dissolution method specified, no Cmax or the timing of the maximum blood levels is provided. The dissolution rates of the 5 active are not appropriate for a suitable chronotherapeutic (see also U.S. Patents 5,376,384 and 5,478,573).

U.S. Patent 5,288,505 and 5,529,791 relate to extended-release galenical formulations of diltiazem or pharmaceutically acceptable salts thereof which comprise beads in which the active ingredient is in association with a wetting 10 agent and which beads are coated by a microporous membrane. The Cmax of some formulations given in the patents provide for a Cmax after about 8-12 hours. Where the dosing of the formulations of the patents yields maximum diltiazem blood plasma levels (Cmax) of about 145 ng/ml, the Cmax is at about or less than 8 hours.

15 The applicants are also aware of a formulation marketed under the trade mark Tiazac™ a diltiazem HCl 24-hour sustained-release formulation based on teachings of U.S. Patent 5,529,791 and 5,288,505.

Following chronic administration of Tiazac (240 mg once daily), the average peak 20 plasma Diltiazem concentration (Cmax) is 183 ng/ml (multiple dosage) which occurred after about 7 hours past dose administration. Tiazac™ provides a bioavailability of approximately 59% of the total Diltiazem in the first 12 hours and 41% in the second 12 hours (after 12 hours, 59%; after 16 hours 77% and after 20 hours 90%).

In an article entitled *Effect of Morning Versus Evening Dosing of Diltiazem on 25 Myocardial Ischemia Detected by Ambulatory Electrocardiographic Monitoring in*

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Chronic Stable Angio Pectoris, PRA KASH, C. Deedwanian et al., The American Journal of Cardiology, Vol. 80, Aug. 15, 1997, p. 421-425, the authors compare a.m. and p.m. dosing without using an appropriate dosage form for p.m. The Tmax is achieved between 2-6 hours at steady state.

- 5 In an article *The Influence of Time Administration on the Pharmacokinetics of a Once A Day Diltiazem Formulation: Morning Against Bedtime*, Jean Thiffault et al., Biopharmaceutics & Drug Disposition, Vol. 17, 107 - 115 (1996), the once-a-day diltiazem formulation given at 2200 hours for seven days gave "significantly higher plasma concentrations of diltiazem in the early morning hours when the
- 10 incidence of cardiovascular events is higher". The diltiazem dosages comprise 240 mg taken at 10:00 p.m. (22:00 hours) and maximum concentrations (Cmax) were achieved of 120 ng/ml after about six - eight hours of dosing. Unfortunately, the proposed system covers the period from 2:00 a.m. to 8:00 a.m. To be a true chronotherapeutic, the time period covered should be between about
- 15 6:00 a.m. and noon. Moreover, this formulation when given at night leads to significantly lower bioavailability than if given in the morning.
- It is therefore an object of this invention to provide diltiazem preparations suitable for once-a-day administration in the evening for providing effective dosage amounts in the blood of diltiazem in the morning when blood pressure
- 20 begins to rise from the low levels reached during sleep, so as to be suitable as a chronotherapeutic preparation.

It is a further object of this invention to provide a method of administration of the diltiazem preparations suitable as a chronotherapeutic so as to be effective in the morning at a time when the patient has most need of the diltiazem preparation.

Further and other objects of the invention will be realized by those skilled in the art from the following summary of the invention and detailed description of embodiments thereof.

SUMMARY OF THE INVENTION

- 5 According to one aspect of the invention, there is provided a controlled-release Galenical preparation (such as a tablet and a capsule) of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, such as the hydrochloride salt, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg or more (as desired) of the form
10 of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (preferably about 11 - about 13 hours) after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the Diltiazem is adapted to be
15 released after administration over a prolonged period of time and the preparation is adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII (at 100 rpm in 900 ml of water):

20 (a) between about 1% and about 15% after about 2 hours,
preferably between about 4% and about 8% after 2 hours;

(b) between about 7% and about 35% after about 4 hours
preferably between about 16% and about 21% after 4 hours;

(c) between about 30% and about 58% after about 8 hours
25 preferably between about 44% and about 52% after 8 hours;

(d) between about 55% and about 80% after about 14 hours
preferably between about 69% and about 76% after about 14 hours;
and

(e) in excess of about 75% after about 24 hours and preferably
more than about 85% after 30 hours.

5 and/or (ii) into a buffered medium (such as, for example, phosphate buffer
(U.S.P.)) having a pH between about 5.5 and about 6.5, preferably about 5.8 at the
following rates measured using the method of United States Pharmacopoeia No.
XXIII at 100 rpm in 900ml of the buffered medium:

10 (a) between about 1% and about 25% after about 2 hours,
preferably between about 4% and about 15% after 2 hours;

(b) between about 7% and about 45% after about 4 hours
preferably between about 16% and about 30% after 4 hours;

(c) between about 30% and about 68% after about 8 hours
preferably between about 44% and about 62% after 8 hours;

15 (d) in excess of about 75% after about 24 hours and preferably
more than 80% after 24 hours.

Preferably no initial retard or delay is built into the preparation retarding
/delaying release of Diltiazem from the preparation. Preferably the release rate

20 from the preparation of the Diltiazem is less than about 15% of the total active
per hour during dissolution. The preparation may be a diffusion controlled
preparation such as, for example, a preparation incorporating the use of
microgranules found, for example, in capsules and tablets; tablets; and coated
tablets.

The preparation may comprise a plurality of microgranules or pellets, each microgranule comprising a central core or bead containing the form of diltiazem coated with a microporous membrane. The microgranules or pellets may be included in a capsule which dissolves when swallowed to release the

- 5 microgranules or pellets. The preparation may also comprise a tablet in which the microgranules have been compressed to form the tablet. When compressed into tablet form, wax placebo beads (as known by persons skilled in the art) are preferably included to absorb the shock placed on the microgranules (core and membrane) during the tableting process. By doing so, the integrity of the
10 microgranules containing the Diltiazem active remains intact and the release rate from the preparation is not affected. The tablet may also be coated or uncoated. The preparation may also comprise a sustained-release tablet coating from which preparation the Diltiazem is released. In this regard, the sustained release coating may be applied (sprayed onto) to each tablet.

- 15 Where the preparation comprises microgranules or pellets (for example) in the capsule or tablet (made, for example, by compressing the microgranules (with preferably wax placebo beads)), the central core may comprise Diltiazem or a pharmaceutically acceptable salt thereof associated with a wetting agent. The Diltiazem may be mixed (in whole or in part) with the wetting agent or may not
20 be mixed with the wetting agent. The wetting agent assists to maintain the solubility of the Diltiazem in each microgranule, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which each of the microgranules of the preparation will meet in the gastrointestinal tract.

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If the Diltiazem and/or pharmaceutically acceptable salt is not mixed with the wetting agent then the microporous membrane should comprise with suitable adjuvants, a water-dispersible or water-soluble polymer (such as HPMC) and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer such as

- 5 Eudragit NE30D (a neutral copolymer of acrylic acid ethyl ester and acrylic acid
methyl ester) which hydrates the microgranule (including core). If the
composition comprises a mixture of the Diltiazem and/or pharmaceutically
acceptable salt with the wetting agent, the microporous membrane is preferably
the same. However, it may also comprise any suitable membrane which gives to
10 the preparation the required dissolution characteristics.

In this regard, the preferred microporous membrane comprises Eudragit NE30D

and hydroxypropylmethylcellulose. This membrane will hydrate the core within the microporous membrane which, for example, may contain diltiazem surrounding a neutral pellet of sugar. The Eudragit NE30D in the membrane

- 15 expands when it encounters gastrointestinal fluid to greater than 365% of its original size (elongation). This expandability of the membrane gives it the ability to hydrate the membrane and core. The mechanism of release is postulated to be that the membrane will swell while the fluids penetrate and hydrate the core and dissolve the diltiazem and wetting agent. This mechanism is, it is thought, 20 driven by the concentration gradient through the membrane (high concentration inside and low concentration outside).

When Eudragit RS and Eudragit RL are combined to form the microporous membrane, the membrane can expand only very little before breakage or fracturing. The reason is that Eudragit RS expands minimally (about 6%) before

- 25 the membrane material breaks or fractures changing its release mechanism from

the core. Thus, the mechanism of release from this membrane is thought to be by "washing" the diltiazem through pores created when a plasticizer incorporated in the membrane is released in the gastrointestinal fluid. The diltiazem at the outer surface of the core would be washed from the core through the pores of the
5 microporous membrane, then the diltiazem next presenting itself to the fluids after "washing" of the uppermost (outermost) diltiazem, and so on.

Instead of the wetting agent, any other suitable dissolution agent may be used to assist the release of the Diltiazem from the preparation. For example, instead of the preferred surface active (wetting) agent (surfactant), an organic acid (such as
10 adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid, tartaric acid and the like) may be incorporated in the core. In this regard, the presence of the organic acid in the core permits the diltiazem in the core to dissolve when the composition passes into the higher pH regions of the gastrointestinal tract of the intestine at which pH diltiazem is much less soluble.
15 One of the membranes which may be used (though not preferred) is the combination of Eudragit RS and Eudragit RL disclosed in U.S. Patent 4,721,619. (See column 1, lines 55-68 and column 2, lines 44-68.) The '619 patent also mentions the use of hydroxypropylmethylcellulose as a water-soluble membrane. The mechanism of release in this case is not by hydration of the core
20 but rather by "washing" the Diltiazem through the pores created in the membrane (for example when the plasticizer in the membrane is released in the gastrointestinal fluid).

The Diltiazem may be present in the core in, for example, the hydrochloride salt form, in which event no dissolution agent may be required in the core.

Suitable preparations such as capsules of the microgranules making up the total Diltiazem active present, may comprise, in the core, Diltiazem hydrochloride between about 50% and about 85% (% w/w of the total preparation (for example, about 69% to about 73%)), a wetting agent (such as sucrose stearate)

- 5 between about 2% and about 25% (% w/w of the total preparation) (for example about 7% to about 8%) together with suitable adjuvants in the core, and in the membrane between about 0.1% and about 2% of the total preparation of water-soluble and / or water-dispersible polymer such as hydroxypropylmethylcellulose (for example about 0.3% to about 0.6%), and
10 between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester (such as Eudragit NE30D) (for example about 7% to about 11%).

The microgranules may also be compressed into tablets using suitable excipients.

- The percentages may be as described above. The tablets may be manufactured,
15 as discussed above, using the microgranules with wax placebo beads and compressing the combination into tablets in the presence of, for example, hydrogenated vegetable oil, sodium starch glycolate and silicone dioxide which have been blended with the microgranules and wax placebo beads before tableting. The tablets may then be coated or uncoated.

- 20 According to another aspect of the invention, a method of treatment of a patient's hypertension and/or angina is provided comprising administration of a preparation of Diltiazem described above, to the patient in the evening for example at about 7:00 - about 11:00 p.m. for effective treatment of the patient's hypertension and/or angina the next morning, for example between about 6:00
25 a.m. and about noon.

Thus a 24-hour diltiazem preparation is provided wherein the Cmax of diltiazem in the blood is provided from about 10-15 hours after administration of a single dosage to a patient or about 9-15 hours after multiple dosages over a number of days and displays the dissolution pattern described above determined according
5 to USP 23, page 1791 using Apparatus 1. Apparatus 1 is described as consisting of the following:

a covered vessel made of glass or other inert, transparent material¹; a motor; a metallic drive shaft; and a cylindrical basket.

The vessel is partially immersed in a suitable water bath of any convenient size that permits holding the temperature inside the vessel at $37 \pm 0.5^\circ$ during the test and keeping the bath fluid in constant, smooth motion. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the smoothly rotating stirring element. Apparatus that permits observation of the specimen and stirring element during the test is preferable. The vessel is cylindrical, with a hemispherical bottom. It is 160 to 175 mm high, its inside diameter is 98 to 106 mm, and its nominal capacity is 1000 mL. Its sides are flanged at the top. A fitted cover may be used to retard evaporation.² The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly and without significant wobble. A speed-regulating device is used that allows the shaft rotation speed to be selected and maintained at the rate specified in the individual monograph, within $\pm 4\%$.

Shaft and basket components of the stirring element are fabricated of stainless steel, type 316 or equivalent, to the specifications shown in Figure 1. Unless otherwise specified in the individual monograph, use 40-mesh cloth. A basket having a
5 gold coating 0.0001 inch (2.5 µm) thick may be used. The dosage unit is placed in a dry basket at the beginning of each test. The distance between the inside bottom of the vessel and the basket is maintained at 25 ± 2 mm during the test.

10 ¹ The materials should not sorb, react, or interfere with the specimen being tested.

15 ² If a cover is used, it provides sufficient openings to allow ready insertion of the thermometer and withdrawal of specimens.
(taken from USP 23)

20 15 According to another aspect of the invention, where the preparations comprise cores wherein the diltiazem is in association with a wetting agent, the wetting agent may be selected from:

sugars;

saccharose, mannitol, sorbitol;

25 20 lecithins;

C₁₂ to C₂₀ fatty acid esters of saccarose, commercialized under the name of sucroesters (Gattefosse, France) or under the name of crodesters (Croda, U.K.) such as sucrose stearate marketed under the trade name of Crodesta; xylose esters or xylites;

25 polyoxyethylenic glycerrides;

esters of fatty acids and polyoxyethylene (Brijs, Renex and Eumulgines, Henkel, RFA);

sorbitan fatty acid esters (Span, Atlas, U.S.A.);

polyglycides-glycerides and polyglycides-alcohols esters (Gelucires, Gattefosse, France)

Metal salts such as NaCl or sodium lauryl sulphate

The microporous membrane may be of any suitable material or combination of materials known in the art. Where the wetting agent is in association with the diltiazem in the core and not mixed therewith, the microporous membrane should comprise a water-soluble or water dispersible polymer or copolymer such as hydroxypropylmethylcellulose and a water-, acid- and base-insoluble polymer such as a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester such as Eudragit NE30D. This enables the bead to be hydrated by the introduction of intestinal fluids into the bead hydrating the bead and therefore mixing the diltiazem and the wetting agent. The membrane itself, because of the fluids passing through the membrane, will swell. This membrane acts differently from membranes which do not swell. These other non-hydratable or swellable membranes may be made-up, for example, of water-soluble or water-dispersible polymers or copolymers and a water-, acid- and base-insoluble polymer such as Eudragit RS which swell less easily (owing to the reduced content in quaternary ammonium groups) and are only slightly permeable to active ingredients. This membrane is best suited for coating cores of Diltiazem mixed with a wetting agent or organic acid.

Among materials which may be used to make the microporous membranes, may be mentioned particularly polyacrylates and polymethacrylates of the Eudragit type, ethyl celluloses such as Ethocels from Dow U.S.A. and Aquacoat of FMC U.S.A., hydroxypropylmethylcellulose, hydroxyethylcellulose and hydroxypropylcellulose.

Additionally, adjuvants may be put in the formulation as required such as plastifying agents (plasticizer), pigments, fillers, lubricants and anti-foaming agents. For example talc and/or magnesium stearate may be used as a lubricant, dibutyl sebacate as plasticizer, titanium dioxide as a pigment, Tween 80 as an emulsifier and silicone oil as an anti-foaming agent.

The amount of the microporous membrane is adjusted to provide the sustained release characteristics described.

DETAILED DESCRIPTION OF EMBODIMENTS

The invention will now be illustrated with reference to the following examples and with reference to the following Figures:

Figure 1: is a graph illustrating the Diltiazem Concentration (ng/mL) in the blood after a specified period after a single dose of a 300 mg Diltiazem capsule preparation made according to an embodiment of the invention.

Figure 2: is a graph illustrating the Diltiazem Concentration (ng/mL) in the blood over a 24-hour period after giving multiple doses of the same 300 mg Diltiazem capsules referred to with respect to Figure 1 but over a number of days.

Figure 3: is a graph illustrating dissolution profiles generated according to USP 23 using Apparatus 1 (baskets) at 100 r.p.m. in 900 ml of water for capsule preparations made according to embodiments of the invention (120 mg, 180 mg, 240 mg and 300 mg of Diltiazem active).

Figure 4: illustrates the dissolution profile of a 120 mg capsule preparation of Diltiazem HCl in water according to USP 23 (Apparatus 1 - baskets) according to an embodiment of the invention.

Figure 5: illustrates the dissolution profile of a 120 mg capsule preparation of Diltiazem HCl in gastric fluid according to USP 23 (Apparatus 1 - baskets) according to an embodiment of the invention.

Figure 6: illustrates the dissolution profile of a 120 mg capsule preparation of
5 Diltiazem HCl in intestinal fluid according to USP 23 (Apparatus 1 - baskets)
according to an embodiment of the invention.

Figure 7: is a graphic comparison of the blood level concentrations of a preparation (240 mg) made according to an embodiment of the invention and Dilacor (240 mg), a 24-hour oral sustained release dosage form of Diltiazem.

10 Figure 8: is a graphic comparison of the blood level concentrations of a preparation (240 mg)made according to an embodiment of the invention and Tiazac (240 mg), a 24-hour oral sustained-release dosage form of Diltiazem.

Preparations were manufactured according to the percentages and constituents set out below:

15	Component	% W/W
(1)	Diltiazem hydrochloride	69 - 73
(2)	Microcrystalline cellulose (Avicel ph101)	8 - 9.5
(3)	Povidone K30	1 - 2
(4)	Sucrose stearate (crodesta F150)	7 - 8
20	(5) Magnesium stearate NF	0.5 - 2.5
(6)	Talc USP	0.5 - 5.0
(7)	Titanium dioxide (USP)	0.15 - 0.3
(8)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(9)	Polysorbate 80 (tween)	0.01 - 0.025
25	(10) Simeticone C emulsion USP (dry of 30%)	0.01 - 0.015

- | | | |
|------|------------------------------|--------|
| (11) | Eudragit NE30 D (dry of 30%) | 7 - 11 |
| (12) | Purified water USP | 0 |

Two Examples of preparations given the above percentages were made as 120 mg and 180 mg strengths of Diltiazem (as the HCl salt) in capsule form.

		<u>Example 2</u>	<u>Example 3</u>
	Strength	Strength	
	120 mg capsule	180 mg capsule	
5	(1) 120.00	(1) 180.00	
	(2) 13.63 - 16.18	(2) 20.44 - 24.27	
10	(3) 1.7 - 3.41	(3) 2.56 - 5.11	
	(4) 11.92 - 13.63	(4) 17.88 - 20.44	
	(5) 0.852 - 4.26	(5) 1.278 - 6.388	
	(6) 0.852 - 8.52	(6) 1.278 - 12.78	
	(7) 0.256 - 0.511	(7) 0.383 - 0.767	
15	(8) 0.511 - 1.02	(8) 0.7665 - 1.533	
	(9) 0.0170 - 0.0426	(9) 0.0256 - 0.0639	
	(10) 0.017 - 0.0256	(10) 0.0255 - 0.383	
	(11) 11.92 - 18.74	(11) 17.886 - 28.106	
	(12) 0	(12) 0	
20	240 mg and 300 mg strength preparations in capsule form of Diltiazem (as the HCl salt) were also prepared having the same percentages. They provide the release patterns shown in Figure 3. The dissolution profiles of all of the strengths were generated from biobatches of capsules using Apparatus 1 (baskets) at 100 RPM in 900 ml of water in accordance with USP 23.		

Less than 20% of the formulation is dissolved after about four hours (for example between about 16%-21%) with less than about 10% dissolved in the first two hours (for example between about 4% - about 8%). Less than about 50% is released after 8 hours (for example between about 44%-52%). Less than about 5 73% is released after 14 hours (for example 69%-76%). Preferably in excess of about 85% is released after 24 hours.

Specifically, samples of 120 mg capsules of Diltiazem HCl (made according to the embodiment of the invention) had the following dissolution profile:

Percent Dissolved - Time Elapsed

10

	2h (%)	4h (%)	8h (%)	14h (%)	24h (%)
	5 8	19 19	49 49	72 72	88 88
	4 5	16 14	32 44	76 69	93 86
	5 6	18 16	50 49	72 73	88 90
	7 6	21 17	54 48	76 72	92 87
	5 8	17 19	51 50	74 74	92 91
	6 7	18 19	52 52	74 75	90 92
Mean (%)	6	18	50	73	90
RSD	21.3	10.5	5.1	2.7	2.6

Samples of 180 mg capsules of Diltiazem HCl (made according to an embodiment of the invention) had the following dissolution profiles:

Percent Dissolved - Time Elapsed

15

Lapsed Time	2h (%)	4h (%)	8h (%)	14h (%)	24h (%)
	8 7	21 20	52 52	76 73	91 89
	6 7	19 20	52 51	76 73	93 90
	5 6	16 18	48 50	72 72	89 90
	6 7	19 18	52 49	76 72	98 88
	7 7	20 19	51 51	73 74	91 91
	8 7	20 21	51 51	74 73	92 91
Mean (%)	7	19	51	74	91
RSD	12.8	7.4	2.5	2.1	1.7

Samples of 240 mg capsules of Diltiazem HCl (made according to an embodiment of the invention) had the following dissolution profiles:

Percent Dissolved - Time Elapsed

	2h (%)	4h (%)	8h (%)	14h (%)	24h (%)
	6 4	19 16	46 48	73 71	86 86
	6 5	18 15	48 45	70 68	85 84
	5 5	18 17	49 49	71 72	86 88
	4 7	16 18	46 48	68 71	83 87
	6 4	18 15	49 50	70 68	84 84
	6 6	18 17	48 48	70 71	85 86
Mean (%)	5	17	48	70	85
RSD	18.5	7.7	2.9	2.3	1.7

5

Samples of Diltiazem HCl capsules 300 mg (made according to an embodiment of the invention) had the following dissolution profile:

Percent Dissolved - Time Elapsed

	2h (%)	4h (%)	8h (%)	14h (%)	24h (%)
	3 4	16 16	46 45	68 67	83 83
	6 5	17 16	49 45	73 67	90 83
	6 5	16 16	46 46	69 68	84 84
	5 5	16 16	46 46	69 69	83 87
	6 4	17 15	46 45	68 68	82 86
	5 5	17 17	46 47	69 70	84 87
Mean (%)	5	16	46	69	85
RSD	13.2	3.8	2.4	2.3	2.8

10

Additionally, the following Dissolution Profiles were obtained for the samples of 120 mg Diltiazem HCl Capsules:

Medium: Water

Hour	Diltiazem HCl Capsules % Dissolved (Average of 12 capsules)	Range [%]	RSD
2	6	4 - 8	17.6
4	18	14 - 21	9.8
8	50	44 - 54	5.1

14	73	69 - 76	2.8
24	90	86 - 93	2.5

Medium: Gastric Fluid

Hour	Diltiazem HCl Capsules % Dissolved (Average of 12 capsules)	Range [%]	RSD
2	5	3 - 6	18.8
4	16	14 - 18	9.0
8	49	47 - 52	3.5
14	73	71 - 75	1.8
24	87	85 - 89	1.5

Medium: Intestinal Fluid

Hour	Diltiazem HCl Capsules % Dissolved (Average of 12 capsules)	Range [%]	RSD
2	5	3 - 7	26.0
4	17	14 - 20	12.0
8	43	40 - 47	6.1
14	64	53 - 69	8.1
24	78	65 - 85	8.1

5

Other Dissolution Profiles were determined of
embodiments of the invention
(Medium - USP Water)

10 Apparatus: USP #1 (baskets) at 100 rpm

Diltiazem 120 mg Capsules

TIME [h]	2	4	8	14	24
vessel 1	5%	19	49	72	88
vessel 2	4	16	52	76	93
vessel 3	5	18	50	72	88
vessel 4	7	21	54	76	92
vessel 5	5	17	51	74	92
vessel 6	6	18	52	74	90
vessel 7	8	19	49	72	88
vessel 8		14	44	69	86
vessel 9		16	49	73	90
vessel 10	6	17	48	72	87
vessel 11	8	19	50	74	91
vessel 12	7	19	52	75	92

MEAN	6%	18	50	73	90
SD	1.3	1.9	2.6	2.0	2.3
RSD	21.3	10.5	5.1	2.7	2.6
RANGE	4 - 8	14 - 21	44 - 54	69 - 76	86 - 93

(Medium - Gastric)

Apparatus: USP #1 (baskets) at 100 rpm
5 Diltiazem 120 mg Capsules

TIME [h]	2	4	8	14	24
vessel 1	3	14	51	74	88
vessel 2	6	17	48	72	85
vessel 3	5	17	49	72	85
vessel 4	5	15	48	72	87
vessel 5	4		47	71	86
vessel 6	6	18	50	72	86
vessel 7		15	49	73	88
vessel 8	4	14	48	71	86
vessel 9	5	17	51	74	88
vessel 10	6	18	52	74	88
vessel 11	6	18		75	89
vessel 12	5	17	50	73	87
MEAN	5	16	49	73	87
SD	0.9	1.5	1.7	1.3	1.3
RSD	19.0	9.0	3.5	1.8	1.5
RANGE	3 - 6	14 - 18	47 - 52	71 - 75	85 - 89

(Medium - Intestinal)

10 Apparatus: USP #1 (baskets) at 100 rpm

Diltiazem 120 mg Capsules

TIME [h]	2	4	8	14	24
vessel 1	7	19	45	67	81
vessel 2	4	14	40	64	79
vessel 3	7	20	47	69	83
vessel 4	5	19	46	68	83
vessel 5		17	41	58	69
vessel 6		17	45	69	83
vessel 7	4	17	40	53	65
vessel 8	5	17	42	65	78
vessel 9	5			58	73
vessel 10	5	17	47	68	85
vessel 11	4	15	44	64	81

vessel 12	4	15	43	64	81
MEAN	5	17	43	64	78
SD	1.2	2.0	2.7	5.2	6.4
RSD	25.9	13.0	6.1	8.1	8.1
RANGE	3 - 7	14 - 20	40 - 47	53 - 69	65 - 85

Briefly, the dosages in Examples 1 (120 mg) and 2 (180 mg) and the 240 mg and 300 mg dosages were manufactured by mixing the core (bead) ingredients (diltiazem, microcrystalline cellulose, povidone, sucrose stearate) by introducing

- 5 the components into a planetary mixer and granulating same and mixing with purified water. The plastic mass was then extruded to provide an extrudate.

The extrudate was subsequently spheronized to produce diltiazem spheres in admixture with the wetting agent. The spheres (cores) were dried in an oven and sieved to the appropriate size cores or beads.

- 10 The membrane was prepared by mixing the hydroxypropylmethylcellulose, titanium dioxide, talc, magnesium stearate, Polysorbate 80 and Simethacone C emulsion and thereafter combined with the Eudragit NE30D and water. The spheronized cores were coated with the appropriate thickness of membrane by spraying the cores, coating same. Thus the cores (beads) were coated with the 15 coating suspension to produce the microgranules or pellets. The microgranules or pellets were then dried.

In more detail the process combines Diltiazem Hydrochloride USP, Microcrystalline cellulose NF (Avicel PH 101), Povidone K30 USP and Sucrose Stearate (Crodesta F160) as follows:

- 20 The following were screened through a 1.9 mm screen and added to a mixer bowl:

Diltiazem

Avicel PH 101

Povidone K30.

To remove large agglomerates, the Crodesta 7.98 kg was screened through a 1.0 - 1.2 mm screen and added to the same mixing bowl. The items were then blended in an AMF blender at 50 RPM. 1 kg of the above dry blend was set aside

- 5 to be used as dusting powder (Diltiazem Dusting Powder). The remainder of the blend was continued to be blended at 50 rpm until adequately granulated. The granulated material was then loaded into the hopper of an extruder (such as EXDCS100 or EXDS 60). The granulation was extruded and without breaking up the extrudate, the extrudate was collected. The extrudate was then spheronized
10 into the cores (beads) of the desired size and were dusted as desired by the Diltiazem Dusting Powder set aside. The beads were then dried by spreading them on trays and drying in an oven set at about 57°C. The Drying Temp. was in the order of 55-60°C for about 12 hours (in the order of 12-16 hours). The dried cores (beads) were sieved to collect those of appropriate size (0.7 - 1.4 mm).
- 15 A Eudragit NE30D and hydroxypropylmethylcellulose coating suspension, was made. The following:

Magnesium Stearate NF

Talc USP

Titanium Dioxide USP

20 Hydroxypropylmethylcellulose 2910 USP (Pharmacoat 606)

Polysorbate 80 NF (Tween 80)

Simethicone C Emulsion USP

and pure water were combined within a Silverson Mixer. Water was first mixed with Polysorbate 80 and the Simethicone. The HPMC was then added, then

25 titanium dioxide, then talc and then the Magnesium Stearate. The mixture was

stored for 2 hours. The Eudragit NE30D was screened through a 0.310 mm sieve and added to the mixture.

The beads were then coated with the suspension by using an Aerocoater™ and spraying the beads (which have been preheated to 26°C) with the coating

5 suspension to achieve the desired thickness (about 0.05 mm). The beads were then dried by spreading on trays and drying at 40-45°C for 10 - 12 hours.

Diltiazem HCl 300 mg capsules made according to an embodiment of the invention were tested in a single dose study to determine their bioavailability, their C_{max} and T_{max}, their rate and extent of absorption. Blood sampling for

10 drug content analysis was carried out at 0.0 (predrug) 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 24, 30, 36, 42 and 48 hours post-drug. Vital sign and 12 - Lead ECG monitoring were conducted at 0 (predrug) 2, 6, 8 and 12 hours post-drug. The following was determined from the plasma study:

15 Mean Pharmacokinetic Parameters for Plasma Diltiazem
(n = 41)

Parameter	1 x 300 mg Mean (%CV)
AUC (0-t)(ng.hr / mL)	2703.83 (36.26)
AUC (0-inf.)(ng.hr / mL)	2786.95 (36.39)
C _{max} (ng / mL)	146.33 (38.43)
T _{max} (hours)	13.17 (14.79)
t _{1/2} (hours)	6.96 (17.56)
K _{el} (hour ⁻¹)	0.102 (15.983)

20 Mean Plasma Diltiazem Concentrations (ng/mL)
(n = 41)

SAMPLE TIME (HOURS)	1 x 300 mg
0.00	0.00 ± 0.00
1.00	0.76 ± 2.20
2.00	4.92 ± 3.87
3.00	10.97 ± 5.92
4.00	20.01 ± 10.77

5.00	33.46 ± 18.39
6.00	70.21 ± 37.03
8.00	95.43 ± 41.50
10.00	110.16 ± 47.43
12.00	132.84 ± 52.04
14.00	139.54 ± 55.11
16.00	126.35 ± 50.23
18.00	105.74 ± 40.86
24.00	62.84 ± 24.20
30.00	43.92 ± 16.94
36.00	25.67 ± 11.46
42.00	13.40 ± 7.37
48.00	7.50 ± 4.46

Mean Pharmacokinetic Parameters for Plasma Diltiazem
(n = 36)

Parameter	Geometric Mean Arithmetic Mean (C.V.)
	1 x 300 mg
AUC (0-t hours)(ng.hr/mL)	2682.87 2872.06 (38.44)
AUC (0-x)(ng.hr/mL)	1955.92 2075.00 (35.63)
AUC (0-infinity)(ng.hr/mL)	2847.57 3055.19 (39.05)
C _{max} (ng/mL)	134.96 144.00 (37.17)
T _{max} (hours)**	13.00 (2.92)
t _{1/2} (hours)*	8.69 (22.85)
K _{el} (hour ⁻¹)*	0.084 (22.860)

5 * These are arithmetic means (CV%).

** This is median (± S.D.).

With reference to Figures 1 and 2, it is clear the 300 mg capsule preparation made according to an embodiment of the invention provides the appropriate Diltiazem 10 blood levels at the appropriate time to be suitable for administration as a chronotherapeutic - being given in the evening to provide effective concentrations of Diltiazem the following morning. This suitability is illustrated with reference to Figures 7 and 8. In Figure 7, the 240 mg Diltiazem preparation

made according to the embodiment of the invention provides elevated blood levels that are effective all morning for effective treatment of the patient with Diltiazem. However, the Dilacor formulation (given either in the evening or the following morning) does not protect the patient from 6:00 a.m. - noon, the more
5 dangerous period.

The same is true with Figure 8. Tiazac given in the morning, does not provide the protection. Further, peak plasma concentrations for Tiazac are achieved after about 7 hours after dose administration.

The preparations according to embodiments may also be made as tablets. The
10 tablets may be made as compressed tablets in the desired strengths (for example 120 mg - 540 mg or more Diltiazem) incorporating the microgranules. The tablets may even be scored to permit division into smaller doses.

Tablets may be made as follows using the microgranules or pellets, wax placebo beads and hydrogenated vegetable oil, sodium starch glycolate and silicone
15 dioxide as follows:

The microgranules of Diltiazem may be the following:

Magnesium Stearate

Talc

Titanium Dioxide

20 Hydroxypropylmethyl-Cellulose 2910

Polysorbate 80

Simethicone Emulsion

Eudragit NE30D

Diltiazem Hydrochloride

25 Microcrystalline Cellulose

Povidone K30

Sucrose Stearate

Purified Water

The wax placebo beads may be the following:

5 Microcrystalline Wax NF

Pregelatinized Starch

Sodium Starch Glycolate

Titanium Dioxide

Carbon Dioxide

- 10 The microgranules, wax placebo beads, hydrogenated vegetable oil, sodium starch glycolate and silicone dioxide may be combined and compressed into the desired strengths of tablets, for example 240 mg, 300 mg and 360 mg tablets.
- Briefly, to form the microgranules, Diltiazem HCl, Microcrystalline Cellulose, Povidone 30, Sucrose Stearate may be mixed to form a "dry blend". A 1 kg portion of the dry blend may be removed and stored in a separate labeled container as the Dusting Powder, for use in subsequent manufacturing steps (if desired). Following the removal of the Dusting Powder, Purified Water is added to the dry blend and mixed to create a plastic mass. The plastic mass is extruded through a 1.0 mm screen to form a spaghetti like extrudate. This extrudate is
- 15 then spheronized into beads. During the spheronization process Dusting Powder is added to dry the beads and provide them with a smooth aspect (if required). The addition of Dusting Powder also prevents the newly spheronized beads from sticking together. The spheronized beads are tray dried for 12 - 16 hours and sieved to select beads that are larger than 0.7 mm and smaller than 1.4
- 20 mm in diameter.

The beads are loaded into a preheated (40 - 45°C) fluid bed Aerocoater. Coating suspension is applied at an amount of 10% by spray coating. The resulting Diltiazem Microgranules (coated beads) are dried for between 10 - 12 hours and the dried coated beads are sieved to select coated beads that are larger than 0.7 mm and smaller than 1.7 mm in diameter.

For the manufacture of the placebo wax beads, Microcrystalline Wax, Pregelatinized Maize Starch, Sodium Starch Glycolate and Titanium Dioxide are mixed in a high shear mixer and heated to 64°C (jacket temperature 70°C). The resulting melt is cooled by the addition of liquid CO₂ to form the solid starters of the pellets. The pellet starters are mixed and the size is increased by the gradual turning of the impeller for a fixed timeperiod (mixing time is directly related to the impeller speed and the time to reach a temperature of 57 ± 2°C). The resulting beads are sieved to select beads larger than 0.7 mm and smaller than 1.4 mm in diameter.

For manufacturing the Diltiazem chronotherapeutic tablets, the placebo wax beads and the microgranules of Diltiazem are blended at a ratio of about 2:3 (placebo wax beads: microgranules of Diltiazem) with Hydrogenated Vegetable Oil (lubricant), Sodium Starch Glycolate (disintegrant) and Silicone Dioxide (lubricant) added. The blend is tableted under low pressure (approximately 6 - 8 Sc) to form the compressed Diltiazem Tablets.

In the compressed tablets, the placebo wax beads serve to absorb the shock placed on the microgranules of Diltiazem during the tableting process. By doing so the integrity of the microgranules remains in tact and the release rate of the diltiazem is not affected.

DRAFT DOCUMENT

As many changes can be made to the embodiments of the invention without departing from the scope thereof, it is intended that all material contained herein be determined as illustrative of the invention and not in a limiting sense.